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10/505,191	06/24/2005	Jeffrey P. Erickson	AIB-09206	5158

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EXAMINER	
PARAS JR, PETER	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 12/06/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/505,191	ERICKSON, JEFFREY P.	
	Examiner	Art Unit	
	Peter Paras, Jr.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-40 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-40 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-40 are pending.

Priority

It is noted that this application appears to claim subject matter disclosed in prior Application No. 60/357,641, filed 2/20/2002. A reference to the prior application must be inserted as the first sentence(s) of the specification of this application or in an application data sheet (37 CFR 1.76), if applicant intends to rely on the filing date of the prior application under 35 U.S.C. 119(e), 120, 121, or 365(c). See 37 CFR 1.78(a). For benefit claims under 35 U.S.C. 120, 121, or 365(c), the reference must include the relationship (i.e., continuation, divisional, or continuation-in-part) of all nonprovisional applications. If the application is a utility or plant application filed under 35 U.S.C. 111(a) on or after November 29, 2000, the specific reference to the prior application must be submitted during the pendency of the application and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior application. If the application is a utility or plant application which entered the national stage from an international application filed on or after November 29, 2000, after compliance with 35 U.S.C. 371, the specific reference must be submitted during the pendency of the application and within the later of four months from the date on which the national stage commenced under 35 U.S.C. 371(b) or (f) or sixteen months from the filing date of the prior application. See 37 CFR 1.78(a)(2)(ii) and (a)(5)(ii). This time period is not extendable and a failure to submit the reference required by 35 U.S.C. 119(e) and/or 120, where applicable, within this time period is

considered a waiver of any benefit of such prior application(s) under 35 U.S.C. 119(e), 120, 121 and 365(c). A benefit claim filed after the required time period may be accepted if it is accompanied by a grantable petition to accept an unintentionally delayed benefit claim under 35 U.S.C. 119(e), 120, 121 and 365(c). The petition must be accompanied by (1) the reference required by 35 U.S.C. 120 or 119(e) and 37 CFR 1.78(a)(2) or (a)(5) to the prior application (unless previously submitted), (2) a surcharge under 37 CFR 1.17(t), and (3) a statement that the entire delay between the date the claim was due under 37 CFR 1.78(a)(2) or (a)(5) and the date the claim was filed was unintentional. The Director may require additional information where there is a question whether the delay was unintentional.

If the reference to the prior application was previously submitted within the time period set forth in 37 CFR 1.78(a), but not in the first sentence(s) of the specification or an application data sheet (ADS) as required by 37 CFR 1.78(a) (e.g., if the reference was submitted in an oath or declaration or the application transmittal letter), and the information concerning the benefit claim was recognized by the Office as shown by its inclusion on the first filing receipt, the petition under 37 CFR 1.78(a) and the surcharge under 37 CFR 1.17(t) are not required. Applicant is still required to submit the reference in compliance with 37 CFR 1.78(a) by filing an amendment to the first sentence(s) of the specification or an ADS. See MPEP § 201.11.

Claim Objections

Claims 36-40 are objected to because of the following informalities: the claims are methods but are directed to polypeptides. Appropriate correction is required.

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 29-40 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to a method of producing a transgenic non-human mammal expressing a polypeptide in saliva at a level of at least 0.5mg/ml.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1117. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1116.

The DNA sequences of all *cis*-acting expression signals necessary for salivary gland expression and saliva-specific expression of a polypeptide of interest encompassed within the genus of salivary gland and saliva-specific cis-acting expression signals have not been disclosed. Based upon the prior art there is expected to be sequence variation among the species of DNA sequences of saliva *cis*-acting elements. The specification contemplates that expression control regions from the gene for parotid secretory proteins generally are suitable to engineer salivary-gland specific gene expression (see page 27). The specification has also contemplated that transcription control elements of genes for rat salivary-gland B1-immunoreactive proteins of adult and neonatal rat sublingual and parotid glands, their homologs and paralogs are suitable to engineer salivary gland, sublingual gland and/or parotid gland-specific expression of genes in accordance with the claimed invention. See page 28. The specification however has not disclosed the sequences of any of the *cis*-acting elements embraced by the claims. There is no evidence on the record of a relationship between the structures of the DNA molecules of any of the embraced *cis*-acting elements that would provide any reliable information about the structure of DNA molecules within the genus. There is no evidence on the record that embraced *cis*-acting elements had known structural relationships to each other; the art indicated that there is variation between DNA sequences of various saliva specific *cis*-acting elements. The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which are not conventional in the art as of applicant's effective filing

date. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998).

In the instant case the claimed embodiments of *cis*-acting elements capable of directing salivary gland expression and saliva-specific expression thereof encompassed within the genus of *cis*-acting saliva elements lack a written description. The specification fails to describe what DNA molecules fall into this genus. The skilled artisan cannot envision the detailed chemical structure of the encompassed regulatory elements, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

In view of the above considerations one of skill in the art would not recognize that applicant was in possession of the necessary common features or attributes possessed

by a member of the genus of *cis*-acting elements capable of directing salivary gland expression and saliva-specific expression. Moreover, the art has recognized that there would be variation among the species of the genus of DNA sequences of saliva specific *cis*-acting element as such elements appear to be specific for particular genes from different salivary cell types. Therefore, Applicant was not in possession of the genus of saliva specific *cis*-acting elements as encompassed by the claims. University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that to fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention."

Claims 1-40 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to a transgenic non-human mammal expressing a polypeptide in saliva at a level of at least 0.5mg/ml, a method of collecting saliva from the same transgenic non-human mammal, and a method of producing the same transgenic non-human mammal.

The specification has asserted that the invention features transgenic non-human mammals that express transgenic polypeptides in their saliva. The specification

discusses that salivary gland and saliva specific regulatory elements are necessary to achieve saliva specific expression of a polypeptide of interest. See pages 26-28 of the specification. However, the guidance provided by the specification does not correlate to use of any particular saliva specific regulatory element for the creation of transgenic non-human mammals embraced by the claims. Moreover, the guidance provided by the specification is general as it does not even disclose which saliva regulatory elements could be used to create any of the transgenic non-human mammals embraced by the claims. Finally, the working examples provided by the specification (see pages 81-101) while exemplifying creation of different transgenic cows that express prothrombin and fibrinogen in their saliva respectively, did not disclose which saliva regulatory elements were used to create the transgenic cows and therefore failed to provide the skilled artisan with adequate guidance to make any of the transgenic non-human mammals embraced by the claims. Given the lack of guidance provided by the specification it would have required undue experimentation for one of skill in the art to make and use the invention as claimed without a reasonable expectation of success.

As a first issue, the claims embrace transgenic non-human mammals that express and produce a transgenic polypeptide in saliva. The specification has discussed that saliva specific regulatory elements are necessary to achieve expression of a polypeptide of interest in saliva of a transgenic non-human mammal. See pages 26-29 of the specification. However, the guidance provided by the specification with respect to use of saliva specific regulatory elements was general and did not specifically relate to use of any particular regulatory sequence. Moreover, the specification while

suggesting that certain regulatory elements (from PSP and B1-Ips genes) could be used failed to disclose the actual nucleotide sequences of such elements, which could direct a high level of transgene expression in saliva. This is an important point because the prior art has set forth that regulatory sequences of genes expressed in the cells of salivary gland are basically undeveloped and failed to direct high levels of polypeptide expression. See Samuelson (Annu. Rev. Phys., 1996, 58: 209-229), for example on page 217, which discussed the limitations of using the "known" promoter sequence of the parotid secretory protein (PSP) gene. Also, Samuelson provided an extensive review of the limitations of known salivary gland promoters. See throughout Samuelson. Finally, in an attempt to provide guidance as to which saliva regulatory sequence may be used within the scope of the claimed invention, the specification has relied on improper incorporation by reference of subject matter that appears to be essential. See the references to Mikkelsen, Larson and Mirels at pages 27-28 of the specification. Applicant is reminded that subject matter essential to the claimed invention may not be incorporated by reference to a non-patent publication. See 37 C.F.R. 1.57(c) and MPEP 608.01(p). Accordingly, given the lack of guidance provided by the specification, the skilled artisan would not know which regulatory sequence to use to achieve saliva specific expression of a polypeptide in a transgenic non-human mammal. Given the lack of guidance provided by the specification it would have required undue experimentation for one of skill in the art to make and use any of the transgenic non-human mammals embraced by the claims without a reasonable expectation of success.

As a second issue, while the claims embrace transgenic non-human mammals expressing a transgenic polypeptide in saliva, the working examples provided by specification did not provide adequate guidance that would enable one of skill in the art to create any of the transgenic non-human mammals embraced by the claims. The working examples (see pages 81-101 of the specification) discussed the creation of separate transgenic cows that expressed prothrombin and fibrinogen respectively in their saliva. However, the working examples failed to disclose which saliva regulatory elements were used in the creation the transgenic cows. As previously stated the specification as a whole has not even identified or provided the regulatory elements necessary to practice the claimed invention. A mere statement that saliva regulatory elements existed and could be used is not sufficient to enable the breadth of the claims as directed to transgenic non-human mammals expressing transgenic polypeptides in saliva. If there is no disclosure of starting material or of any conditions under which claimed process can be carried out, undue experimentation is required, and there is failure to meet enablement requirement that cannot be rectified by asserting that all disclosure related to process is within skill of art. See Genentech Inc. v. Novo Nordisk A/S 42 USPQ2d 1001, 1997. In this case the starting material that has not been disclosed is the saliva regulatory element necessary to create the transgenic non-human mammals embraced by the claims.

As a final issue, the claims embrace transgenic non-human mammals that produce transgenic polypeptides in saliva. As written the claims did not convey germline transmission of the transgene and can be broadly interpreted to read on a

transgenic non-human mammal having a single cell expressing a transgene in saliva. It would be unpredictable if expression of a transgene in a single cell of a transgenic non-human mammal correlated to expression and collection of a transgenic polypeptide in saliva, particularly since expression of a transgenic polypeptide in a single cell would not result in a collectable amount of the polypeptide. Moreover it is unpredictable if a transgenic non-human mammal that expressed a transgene in a single cell could be used in the claimed methods because it would appear that the claimed methods would require the transgene to be expressed in every cell of the salivary gland, in particular because it would be unpredictable if a single cell, which expresses the transgene could produce sufficient levels of a transgenic polypeptide for practicing the invention as claimed, and more particularly because the claims require the transgenic polypeptide to produced at a level of 0.5mg/ml.

Alternatively, the claims may be interpreted to read somatic cell gene transfer, wherein the cells of the salivary glands of non-human mammals have been administered vectors comprising nucleic acid molecules encoding a polypeptide of interest. Such an interpretation of the claims would result in both salivary specific and/or systemic polypeptide expression depending on which promoter is used. The prior art in fact teaches that salivary glands may be used as an entry point for introduction of gene therapy type expression vectors into a subject to obtain systemic expression of therapeutic polypeptides. See Baum et al (Trends in Molecular Medicine, 2004, 10(12): 585-590), for examples on pages 587-588. If for example, the polypeptide of interest is thrombin then systemic expression would probably kill the

transgenic non-human mammal as a result of massive blood clotting throughout the non-human mammal. Therefore it would be unpredictable if transgenic non-human mammals created by somatic cell gene transfer to the salivary gland could be created and used in accordance with the invention as claimed.

It is suggested the claims be amended to convey germline transmission of the transgene. An example of suitable claim language that *may* overcome this aspect of the enablement rejection is as follows: a transgenic non-human mammal whose genome comprises an exogenous nucleotide sequence, etc. Given the lack of guidance provided by the specification for using a transgenic non-human mammal comprising a single cell that expresses a transgenic polypeptide, it would have required undue experimentation for one of skill in the art to practice the invention as claimed without a reasonable expectation of success.

Given, the lack of guidance and absence of working examples provided by the specification correlating to creation of transgenic non-human mammals, the lack of guidance provided by the specification with respect to use of saliva regulatory elements, the unpredictability of saliva regulatory elements, it would have required undue experimentation for the skilled artisan to practice the claimed invention.

Claim Rejections - 35 USC § 112, 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2-4, 14-15, 23, 25-26 and 29-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 is indefinite as written. The claim is directed to a transgenic non-human mammal that comprises a monogastric ruminant. The claim is indefinite as written because it is unclear how a transgenic non-human mammal can comprise another mammal. It is well known that a monogastric ruminant is a mammal. Appropriate correction is required. Claims 3-4 depend from claim 2.

Claims 3, 25, and 31 are indefinite as written. The claims are directed to a monogastric ruminant that comprises a bovine. The claims are indefinite as written because it is unclear how a monogastic ruminant (mammal) can comprise a bovine. It is well known that a bovine is a monogastric ruminant. Appropriate correction is required. Claim 4 depends from claim 3, claim 26 depends from claim 25, and claim 32 depends from claim 31.

Claim 14 is indefinite as written. The claim embraces a salivary gland cell transgene. While the specification has provided a definition for transgene (see page 25) the specification has not provided a definition for salivary gland cell transgene. Given, the definition of transgene provided by the specification the term salivary gland cell transgene has no clear meaning. If according to the specification a transgene need only contain one or more exogenous genetic elements then it is not understood what makes a transgene a salivary gland cell transgene. Appropriate correction is required.

Claim 15 is indefinite as written. The claim embraces a parotid gland cell transgene. While the specification has provided a definition for transgene (see page 25) the specification has not provided a definition for salivary gland cell transgene. Given, the definition of transgene provided by the specification the term parotid gland cell transgene has no clear meaning. If according to the specification a transgene need only contain one or more exogenous genetic elements then it is not understood what makes a transgene a parotid gland cell transgene. Appropriate correction is required.

Claim 23 recites the limitation "protein" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim 29 is indefinite as written. The claim in step (d) embraces a polypeptide transgene. The claim is indefinite because transgenes are nucleic acid molecules and do not comprise polypeptides. Moreover, the specification has related the definition of transgene to a gene but has not provided a definition of a polypeptide transgene. Appropriate correction is required. Claims 30-40 depend from claim 29.

Claim 33 recites the limitation "transgenic polypeptide" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim 39 recites the limitation "transgenic polypeptide" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim 40 recites the limitation "human transgenic polypeptide" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Conclusion

No claim is allowed. The claims appear to be free of the prior art of record but are subject to other rejections.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter Paras, Jr. whose telephone number is 571-272-4517. The examiner can normally be reached on M-Th, 7-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Inquiries of a general nature or relating to the status of the application should be directed to Dianiece Jacobs whose telephone number is (571) 272-0532.

Peter Paras, Jr.

Art Unit 1632

PETER PARAS, JR.
PRIMARY EXAMINER